serve as switches for regulating exogenously introduced genes; and

(b) applying an electromagnetic field to each introduced electromagnetic field response element to induce gene expression in the mammal.--

A marked-up version of the amended claims is attached hereto as **Exhibit 1.**

REMARKS

Claims 1-12 were pending in the subject application. By this Amendment, applicants have amended claims 1,3,6 and 9. Accordingly, upon entry of this Amendment, claims 2,4-5,7-8 and 10-12, and amended claims 1,3,6 and 9 will be pending and under examination.

Applicants maintain that the amended claims raise no issue of new matter and are fully supported by the specification as filed.

Support for amended claim 1 may be found *inter alia* in the specification, as originally filed, on page 4, line 5-12. Support for amended claim 3 may be found *inter alia* in the specification, as originally filed, on page 4, line 5-12; and page 16, lines 20-29. Support for amended claim 6 may be found *inter alia* in the specification, as originally filed, on page 4, line 5-12; and page 17, lines 9-33. Support for amended claim 9 may be found *inter alia* in the specification, as originally filed, on page 4, lines 13-21.

On page 2 of the Office Action, The Examiner stated that the specification has improper references to figures. The Examiner also stated that the Office of Petitions (Paper # 4, 07/27/2001)

required an amendment to the specification canceling all reference to Drawings and/or Figures, when the filing date of 01/25/2001 was granted on the petition filed by the applicant and that appropriate correction is required in response to this Office Action.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have canceled all references to Drawings and/or Figures in the specification.

Objections under 37 C.F.R. §1.75

On page 2 of the July 3, 2002 Office Action, the Examiner stated that applicant is advised that should claims 1,2,5 and 8 be found allowable, claims 9, 10, 11 and 12 will be objected to under 37 C.F.R. §1.75 as being substantial duplicates, respectively, thereof. The Examiner stated that when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. The Examiner alleged that in the instant case, claims 1 and 9 are both drawn to a noninvasive method for gene regulation and have identical scope and that claims 2 and 10 are both drawn to the use of nCTCTn sequences in an HSP70 gene promoter as the electromagnetic field response elements and have identical scope.

The Examiner further alleged that claims 5 and 11 are both drawn to the use of nCTCTn sequences in a c-myc gene promoter as the electromagnetic field response elements and have identical scope and that claims 8 and 12 are both drawn to the application of electromagnetic field at a field strength of about 8uT and a frequency of about 60Hz for a time of about 30 minutes and have identical scope.

In response, applicants assert that claims 1 and 9 do not have identical scope. Claim 1 recites in part, "A non-invasive method for gene regulation during gene therapy comprising the steps of: introducing electromagnetic field response elements into a gene promoter....." Whereas, claim 9 recites in part, " A non-invasive method for gene regulation during gene therapy comprising the steps of: introducing at least one electromagnetic field response element into a gene promoter....." The scope of claim 1, therefore, requires introduction of electromagnetic response elements (plural), whereas, the scope of claim 9 only requires introduction of one (singular) electromagnetic response element. Thus, claims 1 and 9 do not have identical scope.

Applicants also assert that claims 2 and 10 do not have identical scope because claim 2 recites using the method as set forth in claim 1, wherein more than one electromagnetic response elements are being introduced, whereas claim 10 recites using the method of claim 9 wherein one or more electromagnetic response element can be introduced. Thus, claims 2 and 10 do not have identical scope.

Applicants further assert that claims 5 and 11 do not have identical scope because claim 5 describes using the method as set forth in claim 1, wherein more than one introduced electromagnetic response elements are nCTCTn sequences in a c-myc gene promoter, whereas claim 11 recites using the method of claim 9 wherein one or more introduced electromagnetic response elements are nCTCTn sequences in a c-myc gene promoter. Thus, claims 5 and 11 do not have identical scope.

Lastly, applicants assert that claims 8 and 12 do not have identical scope because claim 8 recites using the method of claim 1, whereas claim 12 recites using the method of claim 9. Because the methods of claims 1 and 9 (as mentioned above) are different, claims 8 and 12 do not have identical scope.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these objections.

Rejection Under 35 U.S.C. § 112, first paragraph

On page 3 of the July 3, 2002 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art.

Nature of the Invention and Breadth of the Claims:

The Examiner stated that claims 1-12 are directed to a method of gene regulation during gene therapy by introducing electromagnetic field response elements into a gene promoter and applying an electromagnetic field to the introduced electromagnetic field response elements to induce gene expression, wherein the electromagnetic field response elements are nCTCTn sequences in c-myc promoter or hsp70 promoter. Therefore, the nature of the invention is directed toward gene therapy using an electromagnetic field to induce expression of exogenous nucleic acids during gene therapy.

The Examiner further stated that the claims encompass a method of gene regulation during gene therapy and expression of an exogenous

nucleic acid in the cell of an organism *in vivo*, through the application of electromagnetic field, and thereby cover all organisms including human beings. The Examiner further stated that the claims encompass gene therapy, because the only purpose of the delivery and expression of an exogenous nucleic acid, as disclosed by the specification, is for therapeutic purposes, the claims have a very broad scope, and are not limited to the simple delivery and expression of the exogenous nucleic acids *in vitro*. The Examiner stated that the specification does not disclose any other purpose or utility for the method of the instant invention. The Examiner stated that the claims encompass the application of the said method to the whole organism for the purpose of gene therapy and have a very broad scope.

State of the Art:

The Examiner stated that at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..[11], and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). The Examiner quoted Marshall stating that," difficulties in getting genes transferred efficiently to target cells-and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

The Examiner also quoted Orkin et al. stating in a report to the NIH that,".. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector

systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

The Examiner stated that among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression.

The Examiner also stated that Verma et al. teach that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., supra, page 240, column 2). The Examiner also quoted Verma et al. stating that,".. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., supra, page 240, bridging sentence of columns 2-3). The Examiner argued that the state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

The Examiner also stated that, Jin et al. (1997, Bioelectrochem Bioenerg. Vol. 44, No.1, pages 111-120) teach that efficiency of induction is dependent on the type of cells and the source of cells exposed to the electromagnetic fields (page 112, bridging paragraph of the columns) and same cells from different sources have significantly different cellular morphology, growth characteristics, and responses to TPA and that differences in reactivity are sufficient to result in differences in transcript levels. The Examiner stated that the art at the time of filing

clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In response, applicants assert that at the time of filing (January 25, 2001) many advances have been made in *in vivo* gene therapy. Applicants also assert that the articles the Examiner has cited in support of the Examiner's assertion that in vivo gene therapy is unpredictable are outdated. The most recent articles the Examiner cited were the articles by Verma, et al (1997) and Jin, et al (1997).

In support of applicants' assertion that *in vivo* gene therapy at the time of filing was not unpredictable, applicants submit the article by Wang, et al, "Sustained Expression of Therapeutic Level of Factor IX in Hemophilia B Dogs by AAV-Mediated Gene Therapy in Liver, *The Salk Institute* (February 21, 2000), which is attached hereto as **Exhibit A**. Wang, et al., demonstrated that by injection of a recombinant adeno-associated virus vector encoding canine factor IX under the control of a liver-specific enhancer/promoter led to a long-term correction of the bleeding disorder in hemophilia B dogs. Stable expression at a therapeutic level was detected for over 7 months with few to no side effects.

In response to the Examiner's assertion that one of the factors that the art teaches affect efficient gene delivery and sustained gene expression is anti-viral immune responses, particularly against adenoviral proteins, applicants note that in the article by Rux, et al., "Type-Specific Epitope Locations Revealed by X-Ray Crystallographic Study of Adenovirus Type 5 Hexon," volume 1, No. 1 (2000), and attached hereto as **Exhibit B**, new modified adenoviral vectors have been made which overcome the problem of immune responses.

Amount of Direction Provided and Existence of Working Examples:

The Examiner stated that the prior art teaches a method of gene regulation *in vitro* in cell lines using the electromagnetic field response elements, nCTCTn, from c-myc promoter and hsp70 promoter at field strength of 8uT and 60 Hz. However, the Examiner stated, the prior art does not teach the use of the method for the purpose of gene therapy in whole organisms. The Examiner also stated that the prior art does not teach the usefulness of the method to such levels that a therapeutic effect is obtained. The Examiner stated that in cases where prior art does not teach how to use the method, all the guidance for practicing the invention must come from the specification. The Examiner stated that the specification fails to disclose how long the induced expression of exogenous nucleic acids in the cells of organisms lasts, and whether it is long enough to see a therapeutic effect.

The Examiner stated that the specification teaches the use of the EMREs from c-myc promoter placed upstream of CAT or luciferase reporter constructs that were otherwise unresponsive to EM fields (page 17, line 9), transfection of the HeLa cells with the constructs and exposure to EM fields and teaches significant increases in CAT and luciferase activity in the protein extracts of EM field-exposed transfectants. The Examiner alleged that the specification, however, does not provide any guidance on how this increased activity was measured or quantified in terms of the usefulness of the method for gene therapy and for how long after transfection this effect was observed, and whether repeat inductions were necessary and if so, how frequently they were needed, and the level of gene expression needed to achieve a therapeutic result, such that one of skill in the art would accept that their method would result in a therapeutic outcome and be able to practice the method using the guidance provided in the specification. Furthermore, the Examiner stated, the specification does not provide guidance to overcome the art recognized

unpredictabilities of gene therapy because it lacks correlative evidence between the delivery and expression of a gene and any therapeutic effect. The Examiner stated that while the specification demonstrates the transfection of cell lines *in vitro* using the method of the instant invention, it is not predictable that the results obtained *in vitro* correlate to results expected *in vivo* such that one of skill would have reasonable expectation of obtaining therapeutic levels of expression of any gene of interest. The Examiner then stated that it would require undue experimentation on the part of a skilled artisan to determine the vector, the dosage, frequency and route of administration, to obtain a level of expression that would result in a therapeutic effect.

In response, applicants assert that the specification, coupled with the knowledge and level of skill of the art at the time of filing at the time of application, does enable a method of gene regulation *in vivo* using electromagnetic field response elements. For example, the article by Junkersdorf, et al., "Electromagnetic Fields Enhance the Stress Response at Elevated Temperatures in the Nematode Caenorhabditis elgans, "*Bioelectromagnetics*," (2000) 21:100-106, and attached hereto as **Exhibit C,** reported on a study of the effects of low frequency electromagnetic fields (EMF) in the presence of a second stressor (mild heat shock) on the expression of a lacZ reporter gene under the control of hsp16 or hsp70 promoters in two transgenic strains of *C. elegans*. After exposure using EMFs, expression of the reporter gene was found to be strongly enhanced by the EMF. Thus, *in vivo* gene expression has been shown to be strongly enhanced by EMFs.

In addition, as mentioned above, the article by Wang, et al., (February 21, 2000), reported on an *in vivo* experiment using dogs which demonstrated that injection of a recombinant adeno-associated virus vector encoding canine factor IX under the control of a

liver-specific enhancer/promoter led to a long-term correction of the bleeding disorder in hemophilia B dogs. Stable expression at a therapeutic level was detected for over 7 months with few to no side effects. Wang, et al., also showed that *in vivo* gene expression can be stable and at a therapeutic level. Thus, one of skill would have reasonable expectation of obtaining therapeutic levels of gene expression.

Therefore, due to the working *in vivo* examples showing *in vivo* strong levels of gene expression after exposure to EMF and the state of the art *in vivo* gene therapy experiments showing stable delivery mechanisms and achieving therapeutic results, it would not require undue experimentation for someone ordinarily skilled in the art of obtaining therapeutic levels of *in vivo* gene expression after exposure to electromagnetic fields, at the time the application was filed on January 25, 2001.

Predictability of the Art, Amount of Experimentation and Skill Level of the Artisan:

The Examiner stated that while it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, the Examiner stated when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

The Examiner stated that, although the skill of an artisan in this subject area is considered to be very high, it would require undue

experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples, the Examiner stated, do not provide sufficient guidance to practice the invention as claimed. Therefore, the Examiner stated in the absence of specific guidance and working examples, the use of the claimed method in gene therapy is unpredictable. The Examiner then stated that in such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. The Examiner then stated that in view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation in order to use the invention.

The Examiner then stated that, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DMA into the cells using electromagnetic field induction, the lack of guidance concerning the treatment of any disease using the claimed method of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed method of transfection and expression via electromagnetic field induction for the purpose of gene therapy. Thus, the Examiner stated, the specification does not enable one skilled in the art to use the claimed invention in gene therapy.

In response, applicants assert that the art as of the January 25, 2001 filing date does show achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids. For example, as mentioned above, Wang, et al.,(as of February 21, 2000), demonstrated that injection of a recombinant adeno-associated virus vector encoding canine factor IX under the control of a liver-specific enhancer/promoter led to a long-term correction of the bleeding

disorder in hemophilia B dogs. Stable expression at a therapeutic level was detected for over 7 months with few to no side effects.

In addition, as also mentioned above, Junkersdorf, et al., (as of 2000) studied the effects of low frequency electromagnetic fields (EMF) in the presence of a second stressor (mild heat shock) on the expression of a lacZ reporter gene under the control of hsp16 or hsp70 promoters in two transgenic strains of *C. elegans*. After exposure using EMFs, expression of the reporter gene was found to be strongly enhanced by the EMF.

Furthermore, it is known that gene therapy can be used to treat many different types of diseases. Therefore, the specification by mentioning gene therapy, inherently means that it is a method of treating any genetic disease, and therefore, there is not a lack of guidance concerning the treatment of any disease using the claimed method of the instant invention.

Thus, as of applicant's January 25, 2001 filing date, it would not require undue experimentation for someone ordinarily skilled in the art of using the claimed method for transfection and expression via electromagnetic field induction for the purpose of gene therapy.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these objections.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner stated that claims 1-12 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claims 1 and 9 are indefinite in that the preamble recites gene therapy but there is no step for

introducing the constructs into an animal and expressing an exogenous gene in the animal and that claims 2-8 and 10-12 are rejected insofar as they depend from claims 1 and 9.

The Examiner also stated that claim 3 is indefinite in its recitation of "a number of the nCTCTn sequences is 3". The Examiner stated that there is no antecedent basis for "a number of the nCTCTn sequences" and that claim 4 is rejected insofar as it depends from claim 3.

Furthermore, the Examiner stated, claim 6 is indefinite in its recitation of "a number of the nCTCTn sequences is 8" and that there is no antecedent basis for "a number of the nCTCTn sequences". Finally, the Examiner rejected claim 7 insofar as it depends from claim 6.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have amended claims 1 and 9 to include the step of introducing the constructs into a mammal and expressing an exogenous gene in the mammal. Furthermore, amended claims 1 and 9 are inherently supported by the term "gene therapy in the specification." The American Society of Gene Therapy defines gene therapy as, "The treatment of disease be either replacing damaged or abnormal genes with normal ones, or by providing new genetic instructions to help fight disease. Therapeutic genes are transferred into the patient either though a weakened virus, a non-viral vector, or through directly of delivery of so-called "naked" DNA." A copy of the definition is attached hereto as **Exhibit D**. The Examiner also recognizes that the term "gene therapy" has this meaning when the Examiner states, "The preamble recites gene therapy but there is no step for introducing the constructs into an animal and expressing an exogenous gene in the animal."

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the Examiner's position, claims 3 and 6 have been amended to delete the term "a number of the nCTCTn sequences."

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection Under 35 U.S.C. §102

The Examiner rejected claims 1-12 under 35 U.S.C. §102(a) as being allegedly anticipated by Lin et al. (2001, *Journal of Cellular Biochemistry* vol. 81, pages 143-148).

The Examiner stated that although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art, and the claims do not require that the constructs be introduced into an animal.

The Examiner also stated that Lin et al., teach the use of nCTCTn sequences from c-myc promoter and hsp70 promoter in gene regulation (see abstract, page 143). In particular, Lin et al. teach the use of eight nCTCTn elements from c-myc gene promoter (page 143, right column, first paragraph) placed upstream of CAT or luciferase constructs that were otherwise unresponsive to EM fields (page 143, right column, bottom paragraph) in HeLa cells exposed to 8uT and 60 Hz fields. The Examiner stated that Lin et al. further teach the use of three nCTCTn binding sites from hsp70 promoter and the three nCTCTn sequences from the hsp70 promoter used lie between -230 and -160 (page 143, left column, line 9-12). The Examiner stated that the 900 bp region of c-myc gene promoter used contains eight copies of nCTCTn and extends from -353 to -1257 (page 144, left column, "materials and methods", second paragraph). Thus, the Examiner stated, Lin et al. (2001) anticipated the invention of claims 1-12.

In response, applicants submit a signed letter from Wiley Interscience and attached hereto as **Exhibit E** which states that the article by Lin, et al., (2001) Journal of Cellular Biochemistry

vol. 81, pages 143-148) was actually published online on Wiley Interscience in February of 2001 not December of 2000. Thus, applicants' filing date was prior to the publication of Lin, et al., (2002), and claims 1-12 are not anticipated by Lin, et al. (2001)

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner also stated that claims 1, 5-8, 9, 11, 12 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Lin et al. (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288).

The Examiner stated that although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art and the claims do not require that the constructs be introduced into an animal.

The Examiner also stated that Lin et al. (1994) teach a method of gene regulation by exposing c-myc gene promoter construct operably linked to a CAT reporter gene containing the sequences that lie between -1257 and -353 of c-myc promoter (abstract, page 281; page 287, left column, lines 19-21) to electromagnetic fields of Q\iY and 60 Hz (page 283, right column, bottom paragraph).

The Examiner further stated that the presence of eight nCTCTn sequences is an inherent property of the -1257 to -353 c-myc promoter region. The Examiner stated that the intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. §102 only when it serves to define a structural requirement. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is

generally nonlimiting if it merely recites an inherent property, citing M.P.E.P. §2111.02. In the instant case, the Examiner stated the the prior art structure has all the features required to perform the intended use recited in the claims. The Examiner stated that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

Thus, the Examiner stated, Lin et at. (1994) anticipated the invention of claims 1, 5-8, 9, 11, 12.

In response, applicants point out that Lin et al., (1994) dealt with a method of gene regulation by exposing the c-myc gene promoter, which promoter already **contained** electromagnetic field response elements, to electromagnetic fields. However, the claims in the subject application deal with a method of gene regulation by introducing electromagnetic field response elements into a gene promoter **not having** any electromagnetic field response elements already present. Amended claim 1 in the subject application states,

> "A non-invasive method for gene regulation during gene therapy comprising the steps of: (a) introducing electromagnetic field response elements into a gene promoter not having any electromagnetic field response elements in a mammal to serve as switches for regulating exogenously introduced genes; and (b) applying an electromagnetic field to the introduced electromagnetic field response elements to induce gene expression in the mammal." (Emphasis added)

Lin, et al. (1994), therefore, does not have the same method as the claims in the above-identified application and does not contain all the features required to perform the intended use recited in the claims since the introduction of the electromagnetic field response elements was not inherently present in Lin et al. (1994). Thus, Lin et al. (1994) does not anticipate

the invention of claims 1, 5-8, 9, 11, 12.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claim Rejections - 35 U.S.C. §103

The Examiner stated that this application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Thus, the Examiner stated, applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. §103(c)and potential 35 U.S.C. §102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

In response, applicants note that the subject matter of the various claims was commonly owned at the time the inventions covered therein were made.

The Examiner also stated that claims 1-4, 8-10, 12 are rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Han et al. (1998, Journal of Cellular Biochemistry vol. 71, pages 577-583) and Lin et al. (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288).

The Examiner stated that although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art, and the claims do not require that the constructs be introduced into an animal.

The Examiner further stated that Han et al., teach a method of gene regulation by inducing the hsp70 promoter using magnetic fields of 8uT and 60 Hz (page 578, right column, "magnetic field exposure conditions") wherein the region in the hsp70 promoter responsive to magnetic fields mapped to a domain between -230 and -160 in the promoter (page 581, left column, bottom paragraph).

The Examiner also stated that the presence of three nCTCTn sequences within this domain is an innate property of this sequence and that the intended use of the claimed composition is given patentable weight when making a determination of patentability only when it serves to define a structural requirement. The Examiner also stated that the intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the Examiner stated, the preamble is generally nonlimiting if it merely recites an inherent property, citing M.P.E.P. §2111.02. The Examiner stated that in the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. The Examiner also stated that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

The Examiner stated that Han et al., do not teach the induction of gene expression by introducing EMREs into a gene promoter not having any EMREs. However, the Examiner stated Han et al., teach that the stress response proteins induced by magnetic fields provide cytoprotection (pages 580 and 581, bridging sentence) from both lethal temperatures and anoxia and provide the motivation for using the method for stimulating genes that have a protective effect.

Also, the Examiner stated, Lin et al., (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288) teach a method of gene regulation by introducing c-myc gene promoter construct that contains EMREs that lie between -1257 and -353 of c-myc promoter (abstract, page 281; page

287, left column, lines 19-21) operably linked to a CAT reporter gene and exposure of the construct to electromagnetic fields of 8uT and 60 Hz (page 283, right column, bottom paragraph). Thus, the Examiner stated, Lin et al. (1994) provide the motivation for the use of their method to induce heterologous genes which are otherwise not responsive to EM field induction.

Therefore, the Examiner stated one of ordinary skill would have been motivated to use the hsp70 EMREs of Han et al., in the method of Lin et al., and induce genes that do not otherwise respond to EM field exposure. Also, the Examiner stated, the motivation to do so and the expectation of success were derived from the teachings of Lin et al., (1994) who successfully demonstrated that EMREs can be introduced upstream of genes to be induced that do not otherwise respond to EM field exposure due to lack of EMRE elements in their promoter region.

Thus, the Examiner stated, the claimed method would have been *prima facie* obvious to one of skill at the time of the invention.

In response, applicants assert that the alleged combination of Lin et al. (1994) and Han et al. (1998) do not teach or suggest the claimed invention because the combination does not teach all the limitations of the claimed methods. Han et al. at most relates to a method which introduces a promoter construct that already contains EMREs, and then exposing the construct with the EMREs to magnetic fields. Likewise, Lin, et al., (1994) relates a method which introduces a gene promoter construct that already contains EMREs, and then exposing them to electromagnetic fields. However, the claimed method provides a method of gene regulation by introducing EMREs into a gene promoter construct that does <u>not</u> already contain any EMREs. Thus, even if one skilled in the art were somehow motivated to combine those references, applicant urges that the alleged combination does not teach or suggest the claimed invention of claim 1 because neither reference teaches or suggest adding EMREs

to a gene promoter construct that does not contain any EMREs.

Thus, the claimed method of claim 1 would not have been *prima facie* obvious to one of skill at the time of the invention. While the above discussion was in the context of claim 1 (wherein plural EMREs are introduced), the comments apply equally to claim 9 where at least one EMRE is introduced.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

In summary, in light of the remarks and amendments made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the July 3, 2002 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed fee of $200.00 for a two-month extension of time, is deemed necessary in connection with the filing of this Amendment and Petition For A Two-Month Extension Of Time. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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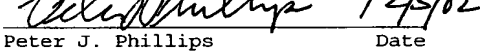

12/3/02

Peter J. Phillips — Date
Reg. No. 29,691

Marked-up Version of Amendments

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

In the Claims:

--1. (amended) A non-invasive method for gene regulation during gene therapy comprising the steps of:

(a) introducing electromagnetic field response elements into a gene promoter not having any electromagnetic field response elements in a mammal to serve as switches for regulating exogenously introduced genes; and

(b) applying an electromagnetic field to the introduced electromagnetic field response elements to induce gene expression in the mammal.--

--3. (amended) The method as set forth in claim 2, wherein [a number of the] three nCTCTn sequences [is 3] in an HSP70 promoter is introduced.--

--6. (amended) The method as set forth in claim 5, wherein [a number of the] eight nCTCTn sequences [is 8] in a c-myc gene promoter is introduced.--

--9. (amended) A non-invasive method for gene regulation during gene therapy comprising the steps of:

(a) introducing at least one electromagnetic field response elements into a gene promoter not having any electromagnetic field response elements in a mammal to serve as switches for regulating exogenously introduced genes; and

(b) applying an electromagnetic field to each introduced electromagnetic field response element to induce gene expression in the mammal.--